OxyContin® (oxycodone HCl controlled-release) Tablets Therapy for Persistent Pain: Clinical Issues, Rationale, & Management Strategy

Preface

This document presents Purdue Pharma's corporate position regarding the management of moderate to severe chronic pain, with a focus on issues regarding prior authorization. It is designed for presentation to Medical Directors, Pharmacy Directors, and Clinical Pharmacists for their consideration in decision-making affecting pain management.

Substance Abuse and Criminal Diversion

Oxycodone, like morphine, fentanyl, and other opioids used for analgesia, can be abused and is subject to criminal diversion.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.[54]

Drug Abuse Warning Network (DAWN) Report

The Drug Abuse Warning Network (DAWN),[53] sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA) in the US Department of Health and Human Services, provides data collected from hospital emergency departments reporting drug-related emergency department (ED) visits induced by or related to substance abuse.[55]

DAWN does not measure the frequency or prevalence of drug use in the population, but rather the health consequences of drug use that are reflected in visits to hospital EDs.[55] The report notes that the following considerations should be weighed when interpreting DAWN estimates:

- The DAWN estimates for 2001 are the first to utilize population data from the 2000 decennial Census. "It is important to note that the population denominator used to calculate rates per 100,000 population is considerably larger for 2001 due to the availability of 2000 decennial Census data. (Estimates for periods prior to 2001 used estimated yearly adjustments from the 1990 Census.) Many large decreases in 2001 population-based rates are attributable to the larger denominator. Therefore, it is important to verify reductions in rates against total estimates for the same measures."[55]

- "The number of ED episodes reported to DAWN is not equivalent to the number of individual patients, because one person may make repeated visits to the ED. DAWN data contain no individual identifiers, which would be required to estimate repeat visits. Therefore, the estimates presented in this publication [2001 ED Trends from the Drug Abuse Warning Network] pertain to total ED episodes or drug mentions, not to the number of different patients involved."[55]

"In this context, rates should be regarded not as prevalence rates for the population using EDs but as indicators of the number of ED drug abuse episodes or mentions per 100,000 population."[55]

- DAWN data may be affected by data collection procedures and thereby reflect changes in hospital services or operations, which may vary over time and place. Estimates of drug-related ED episodes or mentions may also be affected by reporting patterns. For example, a change to computer-based record keeping systems in a hospital ED could increase or decrease the number of ED visits identified as drug related.[53]

- "Greater awareness and knowledge of drug-related problems may result in a greater propensity for ED staff to record drug use in the ED record. Alternatively, the sensitivity of drug-related problems may reduce patients' willingness to disclose drug use and providers' willingness to record it in the permanent medical record."[53]

In 2001, there were 638,484 drug abuse-related ED episodes in the coterminous U.S. with 1,165,367 drug mentions (on average, 1.8 drugs per episode). "Drug mention" refers to a substance that was mentioned during a drug-related ED episode. Because up to 4 drugs and alcohol can be reported for each drug abuse episode, there are always more mentions than episodes cited in the DAWN report.[53]

The four drugs mentioned most frequently in ED reports in 2001 were alcohol-in-combination (218,005 mentions, 18.7% of total mentions), cocaine (193,034 mentions, 16.6% of total), marijuana/hashish (110,512 mentions, 9.48% of total), and heroin (93,064 mentions, 7.99% of total).[53]

DAWN ED mentions of prescription drugs in 2001 were most concentrated in two categories: psychotherapeutic agents (220,289 mentions) and CNS agents (210,685 mentions), representing 19% and 18% of total ED mentions respectively.[53] Taken together, the benzodiazepines, antidepressants, and analgesics constituted 339,484 ED mentions in 2001, or nearly 30% of total ED drug mentions.[53] Overall, mentions of psychotherapeutic agents increased 8 percent from 2000 to 2001, from 204,527 to 220,289. Psychotherapeutic agents in DAWN are broken into 4 subcategories: antidepressants; antipsychotics; anxiolytics, sedatives and hypnotics; and CNS stimulants.[53] Anxiolytics, sedatives, and hypnotics accounted for 12% of total ED mentions (135,949); of these, benzodiazepines accounted for 9% of all ED drug mentions in 2001 (103,972 mentions), a 14% increase from 2000.[53]

Analgesics, with 174,500 ED mentions in 2001, accounted for almost 15% of total ED mentions and approximately 80% of CNS mentions; of these, narcotic analgesics and narcotic analgesic combinations comprised 99,317, representing 8.5% of ED mentions in 2001, almost a 21% increase from 2000.[53]

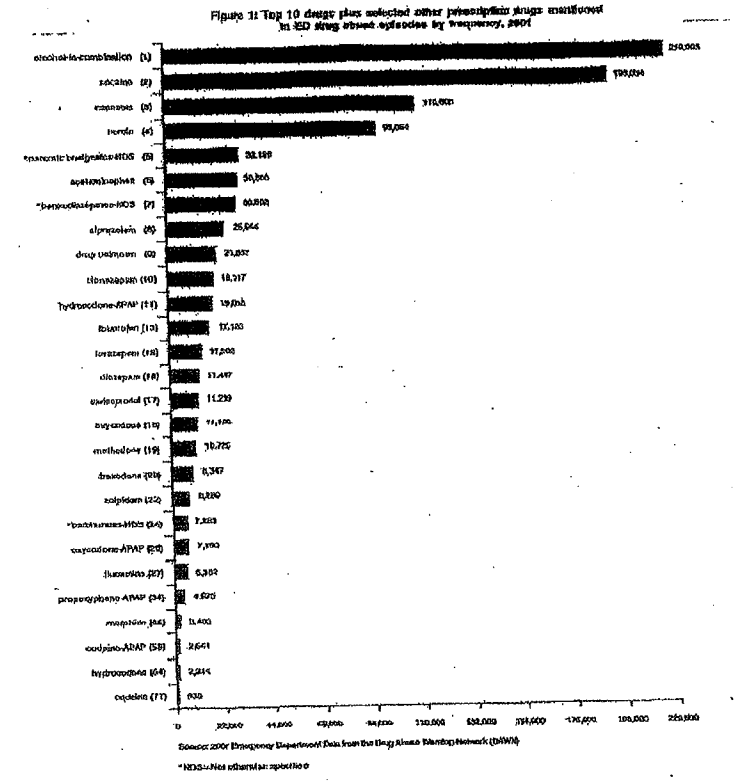


Figure 1: Top 10 drugs plus selected other prescription drugs mentioned in ED drug abuse episodes by frequency, 2001

Source: 2001 Emergency Department Data from the Drug Abuse Warning Network (DAWN)

*NOS = Not otherwise specified

- The prevalence of chronic non-pain related diagnoses was also higher for patients using long-acting opioids than the other two groups.[15]

- In addition to the pain-related etiology, 18.5% of patients taking long-acting opioids had been diagnosed with coronary heart disease; 17.3%, with COPD; 16.3%, with diabetes; 12.0%, with depression; 11.2% with congestive heart failure; and 2.4%, with chronic renal failure.[15]

- Consistent with higher prevalence of medical comorbidities, pain patients taking long-acting opioids were also more likely to have the highest levels of use of adjuvant pain medications. Yet, for all patients, medication costs represented a small proportion of total annual healthcare costs.[15]

- While taking long-acting opioids for 97.2 days (mean), these patients also had taken short-acting opioids for 103.2 days (mean), and such adjuvant pain-related medications as anticonvulsants for 26.2 days (mean); benzodiazepines, 85.6 days (mean); corticosteroids, 17.8 days (mean); muscle relaxants, 29.2 days (mean); NSAIDs, 31.2 days (mean); tricyclic antidepressants, 29.8 days (mean); and SSRI antidepressants, 39.6 days (mean).[15]

- Mean total annual healthcare costs were approximately three times higher among patients taking long-acting opioids, as compared to those taking short-acting opioids. Costs were ten times higher in comparison with patients receiving no opioid analgesics.[15]

- The mean annual costs for patients amounted to

  > $40,083 for patients taking long-acting opioid analgesics

  > $15,750 for patients taking short-acting opioids;

  > $4,390 for patients no taking opioid analgesics.[15]

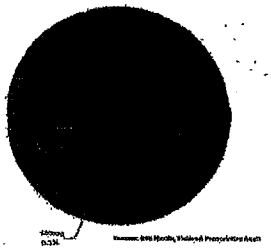
- For all patients, pain-related medication costs represented only a small proportion of total annual healthcare costs.[15]

- Of the $40,083 mean annual costs for patients taking long-acting opioids, outpatient and inpatient services amounted to $37,804. Pain-related medications cost $1,056, which is slightly less than the cost of all other medications – $1,272. The combined medication cost was $2,279, or 5.7% of the total annual cost.[15]

Considerations re: Prior Authorization of OxyContin® (oxycodone HCl controlled-release) Tablets

OxyContin prescriptions accounted for 4.0% of the total opioid prescriptions in OxyContin's defined market category by all prescribers in the most recent calendar year (IMS Health, National Prescription Audit, June 2001-May 2002).[23]

Total OxyContin Rx by Strength,
June 2001-May 2002



- Of the total prescriptions written for OxyContin,
  - > 26.5% are for the 10 mg strength Tablets;
  - > 38.3% are for the 20 mg Tablets;
  - > 25.2%, for 40 mg;
  - > 9.9% for 80 mg;
  - >0.1% for 160 mg.[17]

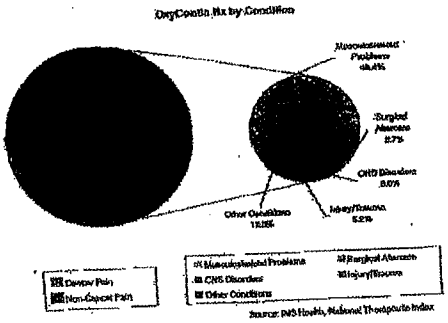
Consideration #1

Of the 174,727,349 prescriptions written for opioid medications over the calendar year June 2001-May 2002, single-entity compounds accounted for 10.7%, while combination opioids accounted for 89.3% of the total.[17]

- OxyContin prescriptions accounted for 4.0% of the total prescriptions written by all opioid prescribers during this period (June 2001-May 2002).[17]

Consideration #2

Prescriptions for OxyContin® (oxycodone HCl controlled-release) Tablets were written for both cancer pain (13.9%) and non-cancer pain (86.1%). The patients without cancer were being treated for pain due to musculoskeletal problems (49.4%), including osteoarthritis, back and neck pain, and joint pain; for surgical aftercare (9.7%); for CNS disorders (8.6%); for injury/trauma (5.2%), and for other conditions (12.5%) (IMS Health, National Disease and Therapeutic Index, January 2001 - December 2001).[78]



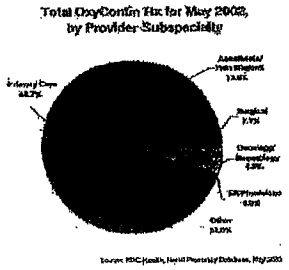
Consideration #3

- In the calendar year June 2001-May 2002, the average number of patients filling a prescription in retail pharmacies for opioids each month was 11,645,521 (NDC Health, Retail Pharmacy Database).[14]
- In the data month May 2002, 11,998,919 patients filled a prescription for opioids in the outpatient setting.[14]
- That month, 49.9% of patients filled prescriptions for hydrocodone combination products, such as Vicodin and Lorcet; 13.0% received codeine combinations such as Tylenol #3 and #4.[14]
- Prescriptions for OxyContin® (oxycodone HCl controlled-release) Tablets were filled by 3.5% of the patients prescribed an opioid.[14]

Consideration #4

- In the data month May 2002, opioids were prescribed for the 11,998,919 patients by the following provider subspecialties: primary care (41.1%), surgical subspecialties (15.0%), ER providers (5.5%), anesthesia/pain management (3.0%), oncology/hematology (1.6%), other subspecialties (33.8%) (NDC Health, Retail Pharmacy Database, May 2002).[14]

- OxyContin® (oxycodone HCl controlled-release) Tablets were prescribed for 422,190 patients by the following provider subspecialties: primary care (48.7%), anesthesia/pain management (13.9%), surgical subspecialties (7.7%), oncology/hematology (4.8%), ER providers (0.9%), other subspecialties, including neurology, endocrinology, and rheumatology (24.0%).[13]

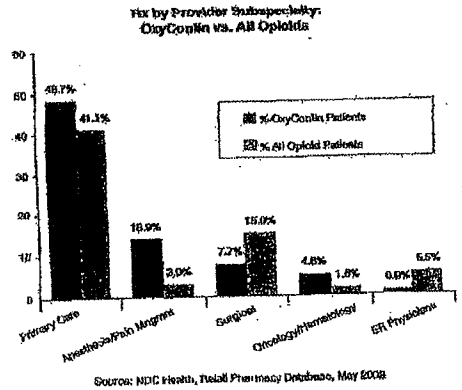


- Although only 3.0% of the total opioid patients received their prescriptions from anesthesiology/pain management, 13.9% of OxyContin patients received their prescriptions from this subspecialty. Indeed, OxyContin patients comprise 16.5% of the total patients prescribed an opioid by this subspecialty.[14]

- Of the total opioid patients, 41.1% received their prescriptions from primary care providers, 48.7% of OxyContin patients received their prescriptions from this group. However, OxyContin patients comprise only 4.2% of the total patients prescribed an opioid by this subspecialty.[15]

- While 15.0% of the total opioid patients received their prescription from a surgeon, only 7.7% of OxyContin patients received their prescriptions from this subspecialty. Indeed, OxyContin patients comprise only 1.8% of the total patients who were prescribed an opioid by a surgeon.[16]

- Although 5.5 % of the total opioid patients received their prescriptions from an ER specialist, only 0.9% of OxyContin® (oxycodone HCl controlled-release) Tablets patients received their prescriptions from an ER doctor. Indeed, OxyContin patients comprise only 0.6% of patients who were prescribed an opioid by an Emergency Room specialist.[14]



Source: NDC Health, Retail Pharmacy Database, May 2008

Conclusion

Given the chronic pain epidemic in the United States and the added health burden that undertreated pain places on patients, a healthcare system's support of effective pain management is vitally important.

In our view, facilitating patient access to pain management therapies without imposing prior authorization specific to OxyContin® (oxycodone HCl controlled-release) Tablets will serve the medical needs of the patients for whom this analgesic is appropriate therapy.

While prior authorization programs may be an effective means of cost minimization and monitoring drug utilization, implementing restrictive guidelines may not only extend the period of suffering for patients, but also lead to greater expenses in the long term due to additional professional and administrative staff time which leads to inefficient pain management and patient care.

If, however, the establishment of such guidelines is deemed necessary, the delay and disruption in patient care may be kept to a minimum if a prior authorization is executed only if the total daily dose of OxyContin tablets is greater than 320 mg.

Under this Prior Authorization (PARx) program, prior authorization is required only if the provider believes that it is appropriate to exceed the 320 mg total daily dose.

As stated above, a total daily dose of 320 mg is equal to 2 x 80 mg OxyContin tablets q12h for patients with the most severe pain and is supported by well-accepted titration principles. This guideline will allow for capturing and conducting prospective drug-use reviews in a subset of patients with the ultimate goal of ensuring appropriate and safe drug therapy.

It is important to recognize that with pure opioid agonist analgesics such as OxyContin, there is no defined maximum dose. Rather, the ceiling to analgesic effectiveness is imposed by side effects, the more serious of which may include somnolence and respiratory depression. During OxyContin clinical trials, certain patients did require total daily doses above 320 mg.

The following information regarding the indications, usage, appropriate dosing and administration of OxyContin® (oxycodone HCl controlled-release) Tablets is important.

Indications and Usage of OxyContin® (oxycodone HCl controlled-release) Tablets

OxyContin is a controlled-release oral formulation of oxycodone HCl indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. OxyContin is not intended for use as a prn analgesic.[50]

Providers should individualize dosage in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.[50]

Dosage Assessment: Individualization of Dosage

Once therapy with OxyContin Tablets is initiated, pain relief and opioid side effects should be frequently assessed. Patients should be titrated to adequate analgesic effect without unmanageable side effects. The appropriate dose of OxyContin, or any other opioid agonist, that is required for an individual patient must be determined on a case-by-case basis by the treating clinician.[50]

During the course of opioid therapy for the treatment of pain, many factors can necessitate an increase or a decrease in the dose of a particular opioid analgesic. These factors can include progression of the disease state causing pain, or possibly tolerance to the analgesic effects of the opioid, or onset of adverse events.[50]

Because steady-state oxycodone plasma concentrations are approximated within 24 to 36 hours, OxyContin dosage adjustment may be carried out every 1 to 2 days for those patients being titrated to adequate pain relief. It is most appropriate to increase the q12 hour dose of OxyContin not the dosing frequency. There is no clinical information on OxyContin dosing intervals shorter than 12 hours.[50]

As a guideline, except for the increase from 10 mg to 20 mg q12 hours, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experience. **Please note that by placing any type of tablet per month limits would not be in compliance with (or would not allow for) the recommended, safe, dose titration as stated in the OxyContin prescribing information.[51]**

Asymmetric Dosing

The analgesic oral dose of OxyContin® (oxycodone HCl controlled-release) Tablets varies widely among individuals. Even though administration (q12h) of OxyContin Tablets in equal (symmetric) morning and evening doses is appropriate for the majority of patients, some patients may benefit from unequal (asymmetric) morning and evening dosing tailored to their pain pattern.[54]

In an open-label study of OxyContin for use up to 18 months in patients with pain associated with osteoarthritis, it was determined that patients titrating their dose upward did so using asymmetric dosing, where either the morning or the evening dose was larger. Of all the patients completing the study (n=21), 37% completed on asymmetric dosing (82% having the larger dose in the morning).[73]

Maximum Daily Doses

With OxyContin, like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia. This is in contrast to mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses.

With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.[54]

In pre-marketing clinical trials, the dose of OxyContin Tablets used by cancer pain patients ranged from 20 mg to over 640 mg per day. In a retrospective review of OxyContin dosage data from 8 clinical trials involving 639 patients with various chronic pain syndromes, 343 (54%) patients took 80 mg or more per day. Of the 343 patients that received at least 80 mg per day, the average daily dose of OxyContin ranged from 80 mg to 1360 mg. When comparing the pain intensity response and the safety profile of this "high-dose group" to that of the entire group (including all dosage ranges), both were similar. The use of higher doses is predicated upon: appropriate patient selection, upward titration to effect, or the development of tolerance to certain physiologic effects of opioids (e.g. respiratory depression).[74]

Please consult the enclosed package insert for the full prescribing information of OxyContin, including the Warnings, Precautions, and Dosage and Administration sections.